

REMARKS

Claims 1, 3, and 5-16 were pending. Claims 10-12 are withdrawn as directed to a non-elected invention. Claims 1, 3 and 5-9 and 13-16 stand rejected. Claims 1 and 13 are hereby amended to remove the term “multivalent.” Support for the amendment is found at page 5, lines 27 to page 6, line 6, which provides a specific example of a non-multivalent vaccine.

Claims 1, 3, and 5 are amended to recite that the denaturation is at higher than about 110°C. Support for the amendment is found at page 29, line 31 to page 30, line 5, in which several heating conditions are provided.

Rejections under 35 U.S.C. § 112

Item 5. Claim 1 is rejected as indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Office Action states that the claimed vaccine is multivalent, implying that multiple antigens from different influenza viruses are present in the composition. The claim also indicates that the composition may comprise only one such antigen, and thereby is unclear.

The claims as amended are not indefinite.

Rejections under 35 U.S.C. §103.

Items 7-8. Applicant thanks Examiner for withdrawal of rejection of claim 1 over Meruelo et al. (U.S. 5,506,271) and claims 3, 5-9, and 13-16 over Meruelo et al. further in view of either Felici et al. (U.S. 5,994,083) or Ooyama et al. (EP 0775 494).

Item 9. Claims 1, 3, 5-9 and 13-16 stand rejected under §103 as obvious over Meruelo et al. in view of Felici et al. or Ooyama et al., further in view of Rios et al. (US 6,383,806) and Lathe et al. (US 6,024,953).

The Office Action states: “The teachings of Meruelo, either alone or in combination with Felici and/or Ooyama, do not teach or suggest the inclusion of such denatured cells in the disclosed immunogenic compositions.” P. 4.

The Office Action relies on Rios (at column 18, lines 5-17) and Lathe (at column 9, lines 41-45) to teach “that antiviral immunogenic compositions may be made both

through the inactivation of the viral antigens, and through inactivation of cells infected with the target virus. ... Moreover, both of these references indicate that the cells may be inactivated by the same process used for the inactivation of the virus itself. In view of these teachings, it would have been obvious to those of ordinary skill in the art that the inactivation step (the heat denaturing in the presence of hypericin) of Meruelo could be applied both against the isolated virus, yielding a composition comprising the denatured viral antigen, or against a virus infected cell, yielding a composition comprising both the denatured viral antigen and the denatured virus-infected cells.” Office Action at p. 4.

The Office Action fails to make a *prima facie* case of obviousness because neither reference teaches *denatured cells*, for the reasons presented below. Rios uses a non-nucleoside inhibitor of HIV-reverse transcriptase for inactivation of the HIV virus. Col. 13, ll. 29-30. Rios inactivates nascent virus in cells, but DOES NOT denature the cells themselves. Col. 18, ll. 5-7. The Rios specification is unambiguous that the reverse transcriptase is used to inhibit HIV and/or nascent HIV, not the host cells. The Office Action fails to provide any information suggesting that HIV-reverse transcriptase can denature cells. Furthermore, one of skill in the art would not presume that reverse transcriptase could denature cells.

Applicant respectfully asserts that one of skill in the art would not, without more, have any expectation that HIV-reverse transcriptase could denature cells.

Unlike the enzymatic process of Rios, the claimed invention uses denaturation at higher than 110 °C. Heat is a known method of cell denaturation.

Lathe uses β -propiolactone to inactivate virus, NOT to denature the cells themselves. Col. 9, ll. 42-46. The Office Action fails to provide any information suggesting that treatment with β -propiolactone denatures cells. Applicant respectfully asserts that one of skill in the art would not expect denaturation of cells using Lathe’s method of using β -propiolactone.

For at least this reason, the rejection should be withdrawn.

Moreover, none of the cited references provide all the elements of the claims as amended. None of the references contemplate denaturation of antigen or immunogen with heat as a primary method. Those references that mention a heat treatment have a only a cursory mention and do not specify the conditions of the instant claims, as amended, which are conditions that *denature* antigens, cells, and immunogens.

The Office Action continues: “Those of ordinary skill in the art would have had a reasonable expectation of success in such an application based on the teachings of Lathe and Rios indicating that the infected cells may be so used, and on the teachings of Meruelo, which indicate that the disclosed methods may be applied with any protein or peptide containing composition.”

Applicant respectfully asserts that there can be no expectation of success where the references do not teach all the elements of the claimed invention. As described above, the references do not teach all the elements of the claims.

Moreover, the Office Action improperly conflates heat denaturation of antigens and cells with chemical treatments, which have vastly different modes of action and result in different products. More specifically, the chemical treatments of Rios and of Lathe are not shown in the references to denature cells.

Furthermore, the references of record do not teach all the elements of the claims as amended, including denaturation of a vaccine, immunogen, or cell at greater than about 110 °C.

For at least the above reasons, withdrawal of the rejections of claims 1, 3, 5-9, and 13-16 over the combination of Meruelo, Felici et al. or Ooyama et al., Rios et al., and Lathe et al. is respectfully requested.

Item 10. Rejection of claims 5-9 as obvious over Yamamoto et al. (US 6,544,528) in view of Meruelo and further in view of either of Felici et al. or Ooyama et al.

The Office Action states that Yamamoto teaches the making of vaccine compositions through the inactivation of either of viruses or of virus-infected cells, that

such cells may be inactivated by heat, and that the vaccine may be formulated for oral administration. Office Action at p. 5.

Yamamoto does not address *denaturation*. Rather, Yamamoto states that “[v]irus and cells in a vaccine formulation may be inactivated or attenuated using ... elevated temperature and the like.” Col. 6, ll. 28-32. Thus, Yamamoto teaches “inactivation or attenuation,” and does not address denaturation. The Office Action does not provide any support that denaturation is the same as inactivation, let alone attenuation. Indeed, one of skill in the art could readily distinguish denaturation, which regards protein structure, from inactivation or attenuation, which can be mild changes resulting from any of many causes.

Moreover, none of the references Yamamoto et al., Meruelo, Felici et al., or Ooyama et al. teach the conditions of denaturation as claimed in the instant invention.

In addition to the fact that the references do not teach all the elements of the claim, the rejection should be withdrawn for an additional reason. The Court has expressly emphasized that it is legally insufficient to conclude that a claim is obvious just because each feature of a claim can be independently shown in the cited art. *KSR Intl Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007). The interdependence of elements of a claim cannot be neglected. A claimed combination of elements is non-obvious if the combination is not a “predictable use of prior art elements according to their established function.” *KSR Intl* at 1740.

The instant claims require a combination of elements that is not appreciated by the prior art.

In particular, claim 5 requires that the immunogen be both *dry* and *denatured at higher than about 110 °C*. The claim also requires that the immunogen comprises *pathogen-infected* and *denatured cells*. In addition, the immunogen is formulated as an oral pill. These elements are interdependent in ways that is not predictable from the references of record. For example, none of the references appreciate the effect of denaturation at higher than about 110 °. Neither Yamamoto, nor Meruelo, nor Felici et

al., nor Ooyama et al. suggest or recognize the consequences of dry denaturation. Meruelo, Felici et al., and Ooyama et al. do not contemplate an immunogen that comprises pathogen-infected cells. Yamamoto teaches inactivation or attenuation of virus or cells rather than the denaturation required in claims 5-9.

Therefore, the assembly of references, none of which teach the interaction of elements claimed in the claims as amended, cannot meet the requirements of the Court as stated in *KSR Intl. Co. v. Teleflex Inc.*

A prima facie case of obviousness requires a showing of motivation to combine the references. The Office Action states that it would have been obvious to combine Yamamoto with the secondary references because Meruelo "indicates that the disclosed method may be applied to any such vaccine composition" and "Yamamoto indicates that the virus infected cells described therein may be inactivated with heat." Office Action at p. 5.

The Office Action does not address the use of dry denaturation. Applicant respectfully asserts that neither Yamamoto nor Meruelo nor Felici et al. nor Ooyama et al. provide motivation to prepare a dry immunogen denatured at higher than about 110 °C according to claims 5-9. Thus, a prima facie case of obviousness has not been established.

For at least these reasons, we respectfully request withdrawal of the rejections of claims 5-9, as amended, over Yamamoto in combination the secondary references of record.

Moreover, Applicant continues to maintain that it is well known in the art that heating an immunogen or protein at temperatures higher than 60 °C, including higher than about 110 °C, causes irreversible changes to the immunogen or protein structure – a process which is known as denaturation. This fact is not only common knowledge but has also been specifically acknowledged by the teachings cited by the Examiner. For this reason, experienced practitioners in vaccine development avoid heating their

compositions at temperatures higher than 60 °C, including higher than 110 °C, and severely limit the duration of exposure to heat in order to avoid the denaturation. Piecing together fragments from several references to form an argument that goes against both common sense and centuries of experience in protein biochemistry is fraught with lack of motivation. The authors of the references or another of ordinary skill in the art could not have expected success of the instant invention based on their own tenuous disclosures in the face of the common practice in the art.

The surprising discovery that the vaccine, composition, and immunogen of the invention are capable of functioning despite being denatured is an aspect of the instant invention that is not addressed by, implied by, or recognized by, the references of record.

For this additional reason, withdrawal of all rejections and allowance of all the pending claims is respectfully requested.

Conclusion

Entry of the amendment is respectfully requested. After entry of the amendment, all pending claims are in condition for allowance.

Applicants have included fees for a three-month extension of time and believe no additional fees are due with this amendment. However, if any additional fees are due, please charge our Deposit Account No. 22-0185, under Order No. 22220-00003-US from which the undersigned is authorized to draw.

The Examiner is urged to directly contact the undersigned at 202-331-7111, if doing so would speed allowance of the claims.

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Respectfully submitted,

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